PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference Case 21733	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/EP2004/006567	International filing date *(day/month/year)* 18.06.2004	Priority date *(day/month/year)* 25.06.2003
International Patent Classification (IPC) or national classification and IPC A61K51/04		
Applicant F. HOFFMANN-LA ROCHE AG		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.12.2004	27.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Dullaart, A Telephone No. +31 70 340-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/006567

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-17 as originally filed

Claims, Numbers

1-11 as originally filed

Drawings, Sheets

1/2-2/2 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/006567

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 11-13

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 11-13 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ the claims, or said claims Nos. 11-13 are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 11-13

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/006567

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-10 .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	8-10

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III.

The International Searching Authority has not searched present claims 11-13 for the following reasons:

Independent claims 11-13 encompass a genus of compounds defined only by their function ("tubulin interactions compound" and "bone-localising radiopharmaceutical"), wherein the relationship between the structural features of the members of the genus and said function has not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognised based upon information readily available to one skilled in the art, the person skilled in the art would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity. Therefore, claims 11-13 do not fulfil the requirements of Articles 5 and 6 PCT.
Claim 13 does not contain any technical feature, and will therefore not be considered.

The present authority will limit the following accordingly.

Re Item IV.

The separate inventions/groups of inventions are:

No.	Claims	Subject
1.	1-4, 6, 9, 10	Tritium labelled MK-0677, and (its use in) a method for identifying a compound that can bind to a growth hormone secretagogue receptor as claimed.
2.	5, 8	Use of tritium labelled MK-0677 for identifying a growth hormone secretagogue receptor, and a method for identifying a growth hormone secretagogue receptor using tritium labelled MK-0677 as claimed.
3.	7	Process of synthesising tritium-labelled MK-0677 as claimed.

No.	Claims	Subject
4.	11-12	Compound according to claim 11, and pharmaceutical composition containing it.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The problem underlying the present application is to provide new radioligands for the growth hormone secretagogue receptor, a process for identifying compounds able to bind this receptor, and/or to act as a growth hormone secretagogue, a process for identifying the growth hormone secretagogue receptor, and a new synthesis for this radioligand. As solution, the present application proposes tritium labelled MK-0677 and its synthesis.

Radiolabelled MK-0677 has, however, already been described in the prior art. In the search report. The applicant already mentions ^{35}S-labelled MK-0677, and in the search report, documents describing ^{14}C-labelled MK-0677 are also mentioned.

Therefore, although the common link between the different problems, i.e., tritiated MK-0677, is novel, this compound does not meet the requirement for inventive step. Rather, it is a mere logical alternative for the existing compound. Like in the previously described documents, the presently claimed compound is labelled in the methylsulfonyl group attached to the nitrogen of the indole ring.

In view of these documents, the technical feature linking the different subjects contained in the present application is no more than a mere combination of features well-known to the person skilled in the art. Therefore, this technical feature can no longer serve as special technical feature in the sense of Rule 13 PCT, linking the different subjects together.
Since there is no other technical feature, that could fulfil the role of special technical feature in the sense of Rule 13 PCT, the present application lacks unity of invention, containing the subject-matters as listed.
However, as the objections for inventions 1-3 are based in the same set of documents, and because invention 4 is not considered to be searchable nor patentable, no further fee is requested from the applicant.

Re Item V.

1 The following documents are referred to in this communication:

D1 : DEAN D C et al: "DEVELOPMENT OF A HIGH SPECIFIC ACTIVITY SULFUR-35-LABELLED SULFONAMIDE RADIOLIGAND THAT ALLOWED THE IDENTIFICATION OF A NEW GROWTH HORMONE SECRETAGOGUE RECEPTOR"
Journal of Medicinal Chemistry, American Chemical Society. Washington, US, vol. 39, no. 9, 1996, pages 1767-1770, XP001018701 ISSN: 0022-2623

D2 : JONES A N et al: "Synthesis, stability, and radiolytic decomposition of carbon-14 labelled MK0677"
Journal of Labelled Compounds and Radiopharmaceuticals, vol. 38, no. 6, 1996, pages 561-565, XP008037025 GB ISSN: 0362-4803

D3 : POMES A et al: "SOLUBILIZATION AND CHARACTERIZATION OF A GROWTH HORMONE SECRETAGOGUE RECEPTOR FROM PORCINE ANTERIOR PITUITARY MEMBRANES"
Biochemical and Biophysical Research Communications, Academic Press Inc. Orlando, FL, US, vol. 225, 1996, pages 939-945, XP001019261 ISSN: 0006-291X

D4 : WO 97/22367 A (PLOEG LEONARDUS V D ; SCHAEFFER JAMES M (US); DEAN DENNIS C (US); SMIT) 26 June 1997 (1997-06-26)

D5 : PONG S-S et al: "IDENTIFICATION OF A NEW G-PROTEIN-LINKED RECEPTOR FOR GROWTH HORMONE SECRETAGOGUES"
Molecular Endocrinology, Baltimore, MD, US, vol. 10, no. 1, 1996, pages 57-61, XP001018700 ISSN: 0888-8809

D6 : NAGAMINE J et al: "Pharmacological profile of a new orally active growth hormone secretagogue, SM-130686"
Journal of Endocrinology, Vol. 171, no. 3, December 2001 (2001-12), pages 481-489, XP002300844 ISSN: 0022-0795

D7 : MATUSZEWSKI B K et al: "Determination of unlabeled and;C-radiolabeled drug candidates in biological fluids using LC-MS-MS - Issues and challenges"
Chromatographia, vol. 52, no. Suppl., 2000, pages S39-S45, XP008037024 ISSN: 0009-5893

D8 : PATCHETT A A et al: "DESIGN AND BIOLOGICAL ACTIVITIES OF L-163,191 (MK-0677): A POTENT, ORALLY ACTIVE GROWTH HORMONE

SECRETAGOGUE"
Proceedings of the National Academy of Sciences of USA, Washington, US, vol. 92, no. 15, 1 July 1995 (1995-07-01), pages 7001-7005, XP000651085
ISSN: 0027-8424

Document **D1** discloses the same structure, but labelled with ^{35}S instead of with ^{3}H. It also describes the same process for its preparation, again with the different radiolabel.
Document **D2** discloses the same structure, but labelled with ^{14}C instead of with ^{3}H. It also describes the same process for its preparation, again with the different radiolabel.
Document **D3** discloses the same structure, labelled with ^{35}S. It also describes a process for identifying other GHS receptor ligands.
Document **D4** discloses the same structure, labelled with ^{35}S. The compound is used in the same methods for identifying receptors and their ligands as in the present application.
Document **D5** discloses the same structure, but labelled with ^{35}S. It also mentions other ligands (labelled with tritium) at page 58, left-hand column. Moreover, page 59, right-hand column mentions tests for verifying the influence of other compounds on the affinity of MK-0677 for the receptors. The results are given in fig. 3 and table 1.
Document **D6** discloses the competitive binding of labelled MK-0677 and SM-130686. The latter is found to have specific and high affinity for the GHS receptor.
Document **D7** discloses also MK-0677, labelled with ^{14}C.
Document **D8** discloses the unlabelled compound.

The presently claimed compounds can be distinguished from the cited prior art by the fact, that they are tritium labelled. However, both **D1** and D2 describe labelled MK-0677. In the case of D1, the compound is labelled with ^{35}S, and in D2 with ^{14}C. Like tritium, these are standard labels for detection. The present authority considers, that the next label of choice, in the present case tritium, would be applied by the skilled person without inventive skills. Thus, claims 1-3 do not meet the requirements of Article 33.3 PCT for inventive step.

With regard to the process of identifying ligands that can bind with the Growth Hormone Secretagogue Receptor (GHSR), the present authority notices the equivalence with the methods described in D3, D5 and D6. Again, replacing one radiolabel by another requires no inventive skills from the person in the art. Thus, claims 6, 9 and 10 do not meet the requirements of Article 33.3 PCT for inventive step.

The GHSR has been identified in D4 using radiolabelled MK-0677. Like in the previous inventions, replacing one radiolabel by another requires no inventive skills from the person in the art. Thus, claims 5 and 8 do not meet the requirements of Article 33.3 PCT for inventive step.

For the synthesis of the labelled compound, reference is again made to D1 and D2. In these documents, the radiolabel is introduced in the compound by the same chemical reaction, i.e., the addition of the methylsulfonyl group. The only difference with the present application is the exact radiolabel. As tritium is rather a usual radiolabel, replacing one radiolabel by another requires no inventive skills from the person in the art. Thus, claim 7 does not meet the requirements of Article 33.3 PCT for inventive step.

Re Item VIII.